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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Stanton L. Gerson
Serial No.	:	09/321,655
Filing Date	:	May 28, 1999
For	:	HEMATOPOIETIC PROGENITOR CELL GENE TRANSDUCTION
Confirmation No.	:	6848
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Examiner	:	Quang Nguyen
Attorney Docket No.	:	CWR-7091NP

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Madam:

In response to the Examiner's Answer mailed January 20, 2012, Appellant presents this Reply Brief.

Amendments to the Appeal Brief begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

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I. STATUS OF CLAIMS

Claims 1and 6 are cancelled.

Claims 2, 3-5 and 7 are finally rejected and hereby appealed.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 3-5 are anticipated under 35 U.S.C. §102(b) by Nolta *et al*. (Blood 86:101-110, 1995) (hereinafter, "Nolta et al") as evidenced by Prockop, D.J. (Science 276:71-74, 1997) (hereinafter, "Prockop") and/or U.S. Patent Application No. US2002/0168765 to Prockop et al. (hereinafter, "the '765 Application").

B. Whether claims 2 and 4-5 are anticipated under 35 U.S.C. §102(b) by Wells *et al*. (Gene Therapy 2:512-520, 1995) (hereinafter, "Wells et al") as evidenced by Prockop and/or the '765 publication.

C. Whether claims 5 and 7 are obvious under 35 U.S.C. §103(a) in view of either Nolta et al. or Wells et al. and Prockop and U.S. Patent No. 5,486,359 to Caplan et al. (hereinafter, "Caplan et al.").

III. ARGUMENTS

Appellant maintains the arguments presented in the Appeal Brief and present the following rebuttal to the positions set forth in the Examiner's Answer.

I. Appellants' reply to Examiner's answer with respect to the 35 U.S.C. §102(b) rejection of claims 3-5 in view of Nolta *et al.* (Blood 86:101-110, 1995) (hereinafter, "Nolta et al") as evidenced by Prockop, D.J. (Science 276:71-74, 1997) (hereinafter, "Prockop") and/or U.S. Patent Application No. US2002/0168765 to Prockop et al. (hereinafter, "the '765 Application")

Appellant argued in the brief on appeal that claim 5 is not anticipated by Nolta *et al.* as evidenced by Prockop and/or the '765 publication, because Nolta *et al.* do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded, as claimed in the present application. Specifically, Appellant notes that Nolta et al. do not teach a homogenous population of human mesenchymal cells that have been isolated, purified, and then culturally expanded from human mesoderm tissue as claimed in the present invention and the claimed isolated, purified and the culturally expanded homogenous population of mesenchymal stem cells are not inherently identical to the stromal cells of Nolta *et al.*

Nolta *et al.* teach that:

> "spicules from unseparated bone marrow were collected by gravity sedimentation and plated in stromal medium… [and then] subconfluent layers of primary stromal cells were split by trypsinization. Stroma was not used as a supporting layer for transduction until passage no. 4. At [that] point, most hematopoietic cells had been eradicated, except for mature macrophages, which comprised less than 1% of the culture, as shown by fluorescence-activated cell sorter (FACS) analysis and immunohistochemical staining for the panleukocyte antigen CD45 using the monoclonal antibody HLE-1 as described. Stromal cells were irradiated (20Gy) and plated at 5 x 10^5 cells per T25 vent-cap flask in

> IMDM/20% FCS the day before use." (Nolta et al., p102, col 1, 2nd full para.).

The result of the isolation technique taught by Nolta *et al*. is a heterogeneous, poorly defined population of marrow derived cells. Nolta *et al*. fail to demonstrate the cell population is a homogenous population of mesenchymal stem cells that has been isolated, purified and culturally expanded.

The Examiner's central argument is essentially that Mesenchymal Stem Cells are present in the mixture of Marrow Stromal Cells that have been passaged 4 times; therefore, Mesenchymal Stems Cells are inherently present in the heterogeneous population without Nolta et al. making specific reference to this cell population. However, these stromal cells are not a homogeneous population, let alone a homogenous population of mesenchymal stem cells as claimed.

As discussed in Prockop, in much of the literature the adherent fibroblastic cells from bone marrow originally described by Friedenstein are termed mesenchymal stem cells or mesenchymal progenitor cells; however, this heterogenous population is recognized by Prockop and other investigators, as being too "crude" to be considered all mesenchymal stem cells. Thus, Appellant once again respectfully puts forth that marrow stromal cells are the heterogeneous population of cells within which the mesenchymal stem cells exist and without isolating, purifying and then culturally expanding such mesenchymal stem cells one cannot arrive at the homogenous population of mesenchymal stem cells recited in present claim 5. Therefore, not all of the claimed limitations have been taught by the cited references and the claims are not anticipated by Nolta *et al*.

In addition, the Examiner asserts that because the claim language does not specify a method of isolation, purification, and culture expansion, the methods of Nolta et al. are covered by the scope of claim 5 (see Examiner's Answer, p. 15, lines 4-6). However, the Examiner must interpret the claims in light of the specification. While it is true that a specific method is not claimed, the specification does explicitly teach that Mesenchymal stem cells for use in a method of the present invention are a distinct population from the more heterogeneous cell population of the marrow stroma, stating that:

> "The hMSCs can be distinguished from the more complex cellular microenvironment present for example in the marrow stroma ("Dexter stroma"). MSCs are distinct in morphology from Dexter stroma and also lack surface markers for T and B lymphocytes, macrophages and endothelial cells." (p. 5, ll. 14-17).

Nolta et al. teach the use of an isolation technique based on adherence of stromal cells to plastic cell culture plates. The only isolation and purification is the removal of non-adherent cells by washing the plates. Therefore, the isolated cells taught by Nolta et al. are not the same homogeneous mesenchymal stem cells that have been isolated, purified, and culture expanded as presently claimed. Accordingly, Appellant respectfully puts forth that the Examiner has failed to demonstrate that all of the claim limitations are taught by the cited prior art references.

In response, the Examiner argues that the term "homogenous" is not defined by the instant specification (see Examiner's answer, p. 13, lines 20-22). However, Appellant notes that the term homogenous as used in present claim 5 is in reference to human mesenchymal stem cells and not to a homologous population of stromal

marrow cells isolated by crude procedures such as those described in Nolta et al. and in Prockop based on the observations of Friedenstein.

Furthermore, Appellant respectfully argues that the term "homogenous" as used in the biological arts is an art recognized term indicating cell populations composed of identical cell types; of the same type, having the same characteristics (see McGraw-Hill Concise Dictionary of Modern Medicine. 2002 by The McGraw-Hill Companies, Inc., attached herewith). Moreover, the term "homogenous" in reference to a population of mesenchymal stem cells that are isolated, purified, and then culturally expanded from human mesoderm tissue would be understood by the skilled artisan in view of the specification as well as the relevant art as a population of cells consisting of or composed of identical cell types; of the same type, having the same characteristics. Specific use of the term "homogenous" in regards to hMSC populations and art recognized homogenous populations of hMSCs in the prior art and can be found, for example, in Caplan et al. cited by the Examiner. Caplan et al. state:

> "Homogeneous human mesenchymal stem cell compositions are provided which serve as the progenitors for all mesenchymal cell lineages. MSCs are identified by specific cell surface markers which are identified with unique monoclonal antibodies. The homogeneous MSC compositions are obtained by positive selection of adherent marrow or periosteal cells which are free of markers associated with either hematopoietic cell or differentiated mesenchymal cells. These' isolated mesenchymal cell populations display epitopic characteristics associated with only mesenchymal stem cells, have the ability to regenerate in culture without differentiating, and have the ability to differentiate into specific mesenchymal lineages when either induced in vitro or placed in vivo at the site of damaged tissue." (Caplan et al. col. 2, first paragraph)

Caplan et al. teach a method of isolating, purifying and culture expanding human mesenchymal stem cells from bone marrow including a cell population having greater than 95% of hMSCs that express SH2, SH3, and SH4 antigens (see Caplan et al., col. 4, paragraph 4). In another example, Pittenger et al. characterized an isolated population of homogeneous human mesenchymal cells obtained from bone marrow. Pittenger et al. reported that isolated cultured mesenchymal cells populations comprised a single phenotypic population (95 and 98% homogeneous at passages 1and 2, respectively) by flow cytometric analysis of expressed surface antigens (see Pittenger et al. Science (1999) 284:143-147, at 144, col. 1, attached herewith). Therefore, Appellant respectfully puts forth that a skilled artisan, in view of the present specification and especially the relevant art would have a clear understanding of the term "homogenous" as recited in present claim 5, specifically in reference to a homologous population of mesenchymal stem cells that are isolated, purified, and then culturally expanded from human mesoderm tissue.

The Examiner further argues in response to Appellant's arguments that the language of claim 7 indicates clearly that the homogenous population of human mesenchymal stem cells in independent claim 5 can contain cells expressing surface markers for T and B lymphocytes, macrophages, and endothelial cells. Appellant fails to see the relevancy of this argument. Once again, Appellant notes that the term homogenous as used in present claim 5 is in reference to human mesenchymal stem cells and not to a homologous population of stromal marrow cells isolated by crude procedures such as those described in Nolta et al. and in Prockop based on the observations of Friedenstein. Furthermore, as stated in the specification, MSCs

for use in a method of the present invention are distinct in morphology from Dexter stroma as the mesenchymal stem cells represent a well characterized cell population which can be prepared in a much more reproducible manner than, for example, the heterogeneous Dexter-like stromal culture. Thus the language of claim 7, which is by law, more narrow than the independent claim upon which it depends, does not indicate in any way that the isolated marrow stroma cells taught by Nolta et al. are equivalent to the homogeneous mesenchymal stem cells that have been isolated, purified, and culture expanded of present claim 5.

The Examiner cites Sylvester et al. stating in part that:

> "One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations…This heterogeneity may be explained by the hypothesis that true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs, and the remainder of the mixed population consists of cell at various stages of differentiation and commitment…" (Examiner's Answer, p. 14, 13-18).

However, this passage further indicates the difference between a homogenous population of mesenchymal cells recited in claim 5 that are isolated, purified and culturally expanded from human mesoderm tissue compared to the crude heterogeneous cell populations produced by Nolta et al.

The Examiner further argues that:

> "Additionally, the ultilized 4th passage cell population can be considered to be homogenous because it is devoid of most hematopoietic cells except for mature macrophages which comprised less that 1% of the culture."(Examiner's Answer, p. 16, lines 1-4).

However, simply because Nolta et al. may teach a homogenous population of marrow stromal cells does not mean that a population of such cells are inherently identical to a population of mesenchymal stem cells of the present invention.

Moreover, there is nothing in Nolta et al. that teaches the passaged stromal cells of Nolta et al. are inherently equivalent to a homogenous population of mesenchymal stem cells. The Examiner infers that mesenchymal stem cells of Nolta et al. are isolated, purified, and expanded by referencing Prockop as support for the presence of mesenchymal stem cells in the adherent cell population. However, Prockop does not support the argument that mesenchymal stem cells have been isolated, purified, and expanded. Contrary to the position taken by the Examiner, Prockop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Friedenstein," *i.e.,* the isolation of marrow stromal cells via adherence to plastic alone that is also used by Nolta *et al.* (see p72, col. 1, para. 3 and col. 2, para. 2). These advantages include that "the isolated cells are either clonal or nearly clonal, they express small amounts of bone cell markers such as alkaline phosphatase, and they can be induced in culture to express large amounts of the same markers…" (p 72, col. 2, para 2).

Therefore, Appellants respectfully submit that the present invention is patentable over Nolta *et al.* as evidenced by Prockop and/or the '765 publication because Nolta *et al.* fail do not teach all the limitations of claim 5. Accordingly, Appellants respectfully request that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn. Claims 3- 4 depend directly from claim 5, and therefore should be

allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitation recited in claims 3-4.

II. Appellants' reply to Examiner's answer with respect to the 35 U.S.C. §102(b) rejection of claims 2 and 4-5 in view of Wells *et al.* (Gene Therapy 2:512-520, 1995) (hereinafter, "Wells et al") as evidenced by Prockop, D.J. (Science 276:71-74, 1997) (hereinafter, "Prockop") and/or U.S. Patent Application No. US2002/0168765 to Prockop et al. (hereinafter, "the '765 Application")

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Wells *et al.* teach:

> "To generate autologous stromal monolayers, cryopreserved marrow from the patient with Gaucher disease was plated at a concentration of 5 x 10^5 cells/ml in tow types of media. The first medium was IMDM with 15% FCS, 15% HS, 10^{-4} M 2-mercaptoethanol, 10^{-6} M hydrocortisone, 50 U/ml penicillin G, 50 µg/ml streptomycin sulfate, and 2 mM L-glutamine. The second medium was IMDM with 10% FCS, 50 U/ml penicillin G, 50 µg/ml streptomycin sulfate, and 2 mM L-glutamine. All of the non-adherent cells were removed 24h after plating. Subconfluent layers of primary stromal cells were split by trypsinization. Stroma was used as a supporting layer for transduction between passages 3 and 5, after hematopoietic cells and macrophages had been depleted. Stromal cells were irradiated (20Gy) and plated at 5 x

> 10^5 cells per T-25 vent-cap flask in transduction medium the day before use." (p518, col. 2, 2nd para).

The result of the isolation technique taught by Wells *et al*. is a heterogeneous, poorly defined population of marrow derived cells. Wells *et al*. fail to demonstrate the cell population is a homogenous population of mesenchymal stem cells that has been isolated, purified and culturally expanded.

The Examiner's central argument is essentially that Mesenchymal Stem Cells are present in the mixture of Marrow Stromal Cells that have been passaged between 3-5 times; therefore, Mesenchymal Stems Cells are inherently present in the heterogeneous population without Wells et al. making specific reference to this cell population. However, these stromal cells are not a homogeneous population, let alone a homogenous population of mesenchymal stem cells as claimed.

As discussed in Prockop, in much of the literature the adherent fibroblastic cells from bone marrow originally described by Friedenstein are termed mesenchymal stem cells or mesenchymal progenitor cells; however, this heterogeneous population is recognized by Prockop and other investigators, as being too "crude" to be considered all mesenchymal stem cells. Thus, Appellant once again respectfully puts forth that marrow stromal cells are the heterogeneous population of cells within which the mesenchymal stem cells exist and without isolating, purifying and then culturally expanding such mesenchymal stem cells one cannot arrive at the homogenous population of mesenchymal stem cells recited in present claim 5. Therefore, not all of the claimed limitations have been taught by the cited references and the claims are not anticipated by Wells *et al*.

In addition, the Examiner asserts that because the claim language does not specify a method of isolation, purification, and culture expansion, the methods of Wells et al. are covered by the scope of claim 5 (see Examiner's Answer, p. 21, lines 1-8). However, the Examiner must interpret the claims in light of the specification. While it is true that a specific method is not claimed, the specification does explicitly teach that Mesenchymal stem cells for use in a method of the present invention are a distinct population from the more heterogeneous cell population of the marrow stroma, stating that:

> "The hMSCs can be distinguished from the more complex cellular microenvironment present for example in the marrow stroma ("Dexter stroma"). MSCs are distinct in morphology from Dexter stroma and also lack surface markers for T and B lymphocytes, macrophages and endothelial cells." (p. 5, ll. 14-17).

Wells et al. teach the use of an isolation technique based on adherence of stromal cells to plastic cell culture plates. The only isolation and purification is the removal of non-adherent cells by washing the plates. Therefore, the isolated cells taught by Wells et al. are not the same homogeneous mesenchymal stem cells that have been isolated, purified, and culture expanded as presently claimed. Accordingly, Appellant respectfully puts forth that the Examiner has failed to demonstrate that all of the claim limitations are taught by the cited prior art references.

In response, the Examiner argues that the term "homogenous" is not defined by the instant specification (see Examiner's answer, p. 13, lines 20-22). However, Appellant notes that the term homogenous as used in present claim 5 is in reference to human mesenchymal stem cells and not to a homologous population of stromal

marrow cells isolated by crude procedures such as those described in Wells et al. and in Prockop based on the observations of Friedenstein.

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Caplan et al. teach a method of isolating, purifying and culture expanding human mesenchymal stem cells from bone marrow including a cell population having greater than 95% of hMSCs that express SH2, SH3, and SH4 antigens (see Caplan et al., col. 4, paragraph 4). In another example, Pittenger et al. characterized an isolated population of homogeneous human mesenchymal cells obtained from bone marrow. Pittenger et al. reported that isolated cultured mesenchymal cells populations comprised a single phenotypic population (95 and 98% homogeneous at passages 1and 2, respectively) by flow cytometric analysis of expressed surface antigens (see Pittenger et al. Science (1999) 284:143-147, at 144, col. 1, attached herewith). Therefore, Appellant respectfully puts forth that a skilled artisan, in view of the present specification and especially the relevant art would have a clear understanding of the term "homogenous" as recited in present claim 5, specifically in reference to a homologous population of mesenchymal stem cells that are isolated, purified, and then culturally expanded from human mesoderm tissue.

The Examiner further argues in response to Appellant's arguments that the language of claim 7 indicates clearly that the homogenous population of human mesenchymal stem cells in independent claim 5 can contain cells expressing surface markers for T and B lymphocytes, macrophages, and endothelial cells. Appellant fails to see the relevancy of this argument. Once again, Appellant notes that the term homogenous as used in present claim 5 is in reference to human mesenchymal stem cells and not to a homologous population of stromal marrow cells isolated by crude procedures such as those described in Wells et al. and in Prockop based on the observations of Friedenstein. Furthermore, as stated in the specification, MSCs

for use in a method of the present invention are distinct in morphology from Dexter stroma as the mesenchymal stem cells represent a well characterized cell population which can be prepared in a much more reproducible manner than, for example, the heterogeneous Dexter-like stromal culture. Thus the language of claim 7, which is by law, more narrow than the independent claim upon which it depends, does not indicate in any way that the isolated marrow stroma cells taught by Wells et al. are equivalent to the homogeneous mesenchymal stem cells that have been isolated, purified, and culture expanded of present claim 5.

The Examiner cites Sylvester et al. stating in part that:

> "One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations…This heterogeneity may be explained by the hypothesis that true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs, and the remainder of the mixed population consists of cell at various stages of differentiation and commitment…" (Examiner's Answer, p. 20, lines 14-19).

However, this passage actually further indicates the difference between a homogenous population of mesenchymal cells recited in claim 5 that are isolated, purified and culturally expanded from human mesoderm tissue compared to the crude heterogeneous cell populations produced by Nolta et al.

The Examiner further argues that:

> "Additionally, the ultilized cell population between passages 3 and 5 can be considered to be homogenous because it is depleated of hematopoietic cells and macrophages."(Examiner's Answer, p. 22, lines 7-9).

However, simply because Wells et al. may teach a homogenous population of marrow stromal cells does not mean that a population of such cells is inherently identical to a population of mesenchymal stem cells of the present invention.

Moreover, there is nothing in Wells et al. that teaches the passaged stromal cells of Wells et al. are inherently equivalent to a homogenous population of mesenchymal stem cells. The Examiner infers that mesenchymal stem cells of Wells et al. are isolated, purified, and expanded by referencing Prockop as support for the presence of mesenchymal stem cells in the adherent cell population. However, Prockop does not support the argument that mesenchymal stem cells have been isolated, purified, and expanded. Contrary to the position taken by the Examiner, Prockop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Friedenstein," *i.e.,* the isolation of marrow stromal cells via adherence to plastic alone that is also used by Wells *et al.* (see p72, col. 1, para. 3 and col. 2, para. 2). These advantages include that "the isolated cells are either clonal or nearly clonal, they express small amounts of bone cell markers such as alkaline phosphatase, and they can be induced in culture to express large amounts of the same markers…" (p 72, col. 2, para 2).

Therefore, Appellant respectfully submits that the present invention is patentable over Wells *et al.* as evidenced by Prockop and/or the '765 publication because Wells *et al.* fail do not teach all the limitations of claim 5. Accordingly, Appellant respectfully requests that the 35 U.S.C. §102(b) rejection of claim 5 be withdrawn. Claims 3- 4 depend directly from claim 5, and therefore should be

allowed because of the aforementioned deficiencies in the rejection with respect to claim 5 and because of the specific limitation recited in claims 3-4.

III. Appellants' reply to Examiner's answer with respect to the 35 U.S.C. §103(a) rejection of claims 5 and 7 in view of Nolta *et al.* (Blood 86:101-110, 1995) (hereinafter, "Nolta et al") or Wells et al. (hereinafter, "Wells et al") as evidenced by Prockop, D.J. (Science 276:71-74, 1997) (hereinafter, "Prockop") and/or U.S. Patent Application No. US2002/0168765 to Prockop et al. (hereinafter, "the '765 Application")

Appellant argued in the brief on appeal that that claim 5 is patentable over either Nolta et al. or Wells et al. in view of Prockop and Caplan et el. because: (1) the Office Action has failed to provide a reasonable rationale to combine either Nolta et al. or Wells et al. with Prockop and Caplan et el. to teach transforming human hematopoietic progenitor cells in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells; and (2) one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of either Nolta et al. or Wells et al. and Prockop and Caplan et el. to transform human hematopoietic progenitor cells in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells.

To overcome the deficiencies in the teachings of Nolta et al. or Wells et al. as to the use of a homogenous population of mesenchymal stem cells for co-culturing human hematopoietic cells that are transformed, the Examiner concludes:

> "an ordinary skilled artisan would have been motivated to modify the teachings of either Nolta et al. or Wells et al. …because Prockop already noted that the adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts; and an isolating and purifying method for a homogenous population of human bone marrow mesenchymal

> cells expressing uniformly SH2, SH3, and SH4 surface antigens was already taught by Caplan et al." (Examiner's Answer, p. 27-28)

Once again, Appellant fails to see the relevance of this statement as to why one skilled in the art would use a homogenous population of mesenchymal stem cells for co-culturing human hematopoietic cells that are transformed. This statement merely notes two facts: (1) Prockop taught "adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts"; and (2) that Caplan et al. taught "isolating and purifying method for a homogenous population of human bone marrow mesenchymal cells expressing uniformly SH2, SH3, and SH4 surface antigen". This statement however does not provide a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

The Examiner once again has merely noted two facts in Prockop and Caplan et al. and has failed to provide the required reasonable rationale as to "why" a skilled artisan would combine these teachings with the teachings of Nolta et al. or Wells et al. to co-culture human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue.

Furthermore, Appellant notes that the Examiner has not identified in the Examiner's answer any reason which would have prompted the ordinary artisan to select a population of isolated, purified, and culturally expanded human mesenchymal stem cells. Accordingly, the Office Action has failed to provide a

reasonable rationale as to why a skilled artisan would transform human hematopoietic progenitor cells with a polynucleotide comprising exogenous genetic material encoding a protein in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells.

Furthermore in regards to claim 7, this passage indicates the unique characteristics of the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells recited in claim 7 compared to mixed population of cell included in the heterogeneous feeder cell populations of Nolta et al. and Wells et al.

As discussed above, Appellant argued in the brief on appeal that one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of either Nolta et al. or Wells et al. and Prockop and Caplan et el. to transform human hematopoietic progenitor cells in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells.

In response, the Examiner argues that:

> "First, there is nothing that is unpredictable or unexpected for the method as claimed. This is because both Nolta et al. and Wells et al. already successfully demonstrated the use of the 4th passage human allogeneic bone marrow stromal cell population and the autologous human bone marrow stromal cell population…depleted of hematopoietic cells and macrophages; respectively, and which contains a homogenous population of human mesenchymal stem cells as already discussed extensively above to support the transduction of human bone marrow CD34+ stem cells in the presence of a recombinant vector." (Examiner's Answer, p. 29-30).

Appellant respectfully disagrees. The cited prior art of Nolta et al. and Wells et al. merely teaches methods for transduction of hematopoietic stem cells on stromal feeder cells. Prockop teach that several groups have attempted to prepare more homogeneous populations of marrow stromal cells. However, a caveat to this teaching is that none of the protocols had been used in more than one laboratory, and it had not been shown whether they isolate the same cells (Prockop, p.72, col. 2, paragraph 2). The Examiner has not presented sufficient evidence that there was an indication that any of these potential isolated cell types are indeed the MSCs of the present invention, nor has the Examiner presented sufficient evidence that a skilled artisan would predict successful transduction using the MSCs of the present invention. Therefore, the solution found in the present invention is not "predictable" as required for a determination of obviousness. Further, the Examiner has not presented any evidence that the MSCs of the present invention had an established function in HSC transduction at the time of invention that would suggest the success of the presently claimed invention.

The Examiner argues in response that the Examiner's position is further supported by the instant specification which states specifically that "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells that exhibit transduction efficiencies, cell expansion and drug resistance comparable to the levels produced in Dexter Stroma and FN enhanced transduction" (original emphasis added by Examiner), and that Dexter Stroma was derived from adhered bone marrow mononuclear cells that were passaged once. The Examiner concludes that these statements indicate that a

much less purified, much less homogenous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in the present invention.

However, the statements cited by the Examiner were not intended to, nor do they illustrate that the cell populations of Dexter Stroma and the MSCs isolated from human mesoderm tissue are substantially identical cell populations. This statement was merely included in the present application to illustrate the effectiveness of the present invention in relation to other methods of *ex vivo* gene transfer into human hematopoietic progenitor cells known at the time of the present invention.

Furthermore, as discussed in Prockop, although the cells isolated with several of the protocols attempting to prepare more homogenous populations differentiate into osteoblasts in culture, it has not been demonstrated that they retain all of the multipotential properties of MSCs isolated by Friedenstein's protocol, such as the potential for differentiating into adipocytes, chondrocytes and myotubes (see Prockop p. 72, col. 2, paragraph 2). Thus, as evidenced by Prockop, it was uncertain at the time of the invention whether or not more homogenous populations of mesenchymal stem cells of the present invention (*i.e.,* isolated, purified, and culturally expanded human mesenchymal stem cells) retained all of the functional properties (*e.g.,* function in HSC transduction) of MSCs isolated by Friedenstein's protocol.

Therefore, one skilled in the art could not infer, find it predictable, and/or have a reasonable expectation of success that the MSC populations recited in claim 5 would be effective in a method for transforming hematopoietic progenitor cells to

express a protein. Accordingly, claim 5 is not obvious in view of Nolta et al., Wells et al., Prockop and Caplan et al.

In response to the Examiner's argument that Appellants only considered each of the above cited references in isolation from the others, Appellants note that ascertaining the differences between the claimed invention and the prior art is one of the factors in determining whether a given claim is non-obviousness in view of the cited art. *KSR v. Teleflex*, 550 U.S. 398, 406 (2007), citing *Graham v. John Deere Co. of Kansas City*, 383 U. S. 1, 17–18 (1966). Thus, making the above observations as to the failure of the cited references to teach or suggest to one of ordinary skill each and every claim limitation recited in claims, is not attacking the references individually. Instead, the observations made above are meant to point out the shortcomings of the disclosures of Nolta *et al.*, Wells et al., Prockop, and the '765 Application alone, as well as in combination, as it relates the claimed subject matter and specifically to point out that Caplan et al. do not provide a reason to combine the cited references to arrive at the claimed invention.

In response to the Examiner's argument that Prockop indicates that at the filing date of the present application, a skilled artisan could prepare MSCs by various methods, including the "crude" method of Friedenstein (see Examiner's Answer, p. 30, second paragraph). Appellant fails to see the relevancy of this argument. While Prockop may teach various methods of preparing MSCs, Prockop does not teach that a homogenous MSC populations recited in claim 5 would be effective in a method for transforming hematopoietic progenitor cells to express a protein.

Please charge any deficiency or credit any overpayment in the fees for this Appeal Brief to our Deposit Account No. 20-0090.

Respectfully submitted,

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IV. CLAIMS APPENDIX

Claim 1 (Cancelled)

Claim 2 (Finally Rejected): The method of claim 5, wherein the mesenchymal stem cells are autologous to the hematopoietic progenitor cells.

Claim 3 (Finally Rejected): The method of claim 5, wherein the mesenchymal stem cells are allogeneic to the hematopoietic progenitor cells.

Claim 4 (Finally Rejected): The method of claim 5 further comprising separating the transformed human progenitor cells from the mesenchymal stem cells.

Claim 5 (Finally Rejected): A method for transforming hematopoietic progenitor cells to express a protein, comprising co-culturing human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue, and transforming the human hematopoietic progenitor cells with a polynucleotide comprising exogenous genetic material encoding a protein in the presence of the isolated, purified, and culturally expanded human mesenchymal stem cells, wherein said protein is expressed.

Claim 6 (Cancelled)

Claim 7 (Finally Rejected): The method of claim 5, the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells.

V. EVIDENCE APPENDIX

In addition to the Evidence cited in the Appellant's brief, the following evidence relied upon by Appellant in response to the Examiner's answer is provided.

1. Definition of "homogenous", McGraw-Hill Concise Dictionary of Modern Medicine. 2002 by The McGraw-Hill Companies, Inc. (see http://medical-dictionary.thefreedictionary.com/p/homogeneous) visited March 20, 2012, print copy attached herewith.

2. Pittenger, M., Mackay, A., Beck, S., Jaiswal, R., Douglas, R., Mosca, J. Moorman, M., Simonetti, D., Craig, S., Marshak, D., *Multilineage Potential of Adult Human Mesenchymal Stem Cells.* Science (1999) 284:143-147, at 144, col. 1, copy attached herewith.